REMARKS

Following this amendment, claims 2, 3, 5, 7, 9-22, 24 and 26 are pending in this application.

1. Claim Amendments

Claim 2 now recites "isolated" extracellular portion, with support for this amendment found on at least page 4, line 24. Claim 7 has been amended to refer to an immunoconjugate of the extracellular portion with an "immune epitope". Specification support for this amendment can be found on page 4, line 1, for example. Claims 22 and 24 now refer to a "composition", rather than a "vaccine", with support for this amendment found on at least page 5, lines 1-3. Claim 23 has been incorporated in claim 22, claim 25 has been incorporated in claim 24 and claim 27 has been incorporated in claim 26. Therefore, claims 23, 25 and 27 have been canceled.

2. The Restriction Requirement under 35 USC §121

The Examiner has required restriction to one of the following inventions under 35 USC §121:

Group I: claims 2, 3, 5, 7 and 22-27 drawn to an extracellular domain of HER2 and vaccines; and

Group II: claims 9-21 drawn to DNA and a method of expression.

The Examiner admits that Groups I and II are related as process of making and product made, but states that Groups I and II are patentably distinct because the protein can be made by recombinant technology, cleavage of the natural protein or by chemical synthesis. The Examiner also urges that DNA and proteins are physically, chemically and biologically distinct and capable of separate manufacture, use and sale. Therefore, the Examiner has called for a restriction to either Group I or Group II.

Applicants hereby confirm their earlier provisional election of Group I, with traverse. The restriction requirement is submitted to be improper as regards the separate treatment of Groups I and II.

Under 35 USC §121, restriction may be required if "two or more independent and distinct inventions are claimed in one application." According to the interpretation provided in MPEP §802.01, the term "independent" means that "there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation or effect . . .." The term "distinct" is defined in MPEP §802.01 as meaning that "two or more subjects as disclosed are related . . . but are capable of separate manufacture, use or sale as claimed, and are patentable (novel and unobvious) over each other . . .."

The above-cited language of 35 USC §121 is clear in that the requirement to restrict an application to one of the inventions disclosed therein is proper only if the disclosed inventions are both independent and distinct. The lengthy explanation provided in MPEP §802.01 of why restriction can

be properly required among independent or distinct inventions is in contradiction to the plain language of the statute and the related rules (37 CFR §1.141). Accordingly, the restriction practice based upon the alternative use of these terms is questionable.

However, even if one accepts the MPEP's interpretation of 35 USC §121, the mere existence of two or more independent or distinct inventions in one application is not sufficient to justify a restriction requirement. According to the guidelines in MPEP §803, if "the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions."

It is submitted that the inventions of Groups I and II as hereinabove defined are not independent. These inventions are all respectively related as protein, and method of making the protein, including the nucleic acid, vector, and host starting materials. Although they might be classified in different subclasses for searching purposes, a search of all the claims directed to the protein, and its encoding nucleic acid is not a serious burden on the Examiner. The inventions of a protein, and its nucleic acid are manifestly close in their relationship. Examiners routinely examine together claims covering a protein and at least one of its methods of preparation. From their intimate and intertwined relationship, it is clear that the inventions represented by Groups I and II are not independent.

With respect to the search required to determine the patentability of the inventions defined by the claims of Groups I and II, applicants represent that it is impossible to conduct an exhaustive search for a defined protein without considering the art disclosing its nucleic acid. Accordingly, performing the entire search covering the protein as well as its encoding nucleic acid is less burdensome on the Examiner than the separate search, which necessarily involves duplication of searching efforts.

In view of the foregoing arguments, the Examiner is requested to reconsider and withdraw the restriction requirement under 35 USC §121.

3. The Rejection under 35 USC §101

Claim 2, and claim 24 dependent thereon, are rejected under 35 USC §101 on the basis that the claimed invention is allegedly directed to nonstatutory subject matter. In order to obviate the rejection, claim 2 has been amended to recite the "isolated" extracellular portion, thus rendering the rejection moot. Applicants respectfully request that the rejection be withdrawn in light of the amendment.

4. The Rejection under 35 USC §101

The Examiner has rejected claims 2, 3, 5, 7 and 22-27 under 35 USC §101 as allegedly lacking utility. The Examiner asserts that the evidence of record does not establish that the invention is useful

outside of a fundamental research setting or for further experimentation; citing MPEP 608.01(p) and *Brenner v Manson*, 383 U.S. 519, 148 USPQ 689 (1966). Applicants rigorously traverse this rejection.

Applicants submit that the extracellular portion does have a definite and currently available utility and that the invention of *Brenner v Manson* can be distinguished from the invention of the above-mentioned application. As mentioned on page 3, lines 14-16 of the application, the ligand for the $p185^{HER2}$ receptor can be isolated and characterized using the purified extracellular domain as set forth in the claims. The ligand for $p185^{HER2}$, called "heregulin", has subsequently been identified and is disclosed in WO 92/20798 (copy attached). This ligand for the $p185^{HER2}$ receptor is clearly useful in its own right for use in quantitative diagnostic assays; for use as a growth factor for *in vitro* cell culture and *in vivo* to promote the growth of cells expressing $p185^{HER2}$ (see page 46, lines 35-38 of WO 92/20798); and for the manufacture of antibodies against heregulin (see page 4, line 24, of WO 92/20798). Such anti-heregulin antibodies are useful for diagnostic assays for detecting heregulin expression and for the affinity purification of heregulin from recombinant cell culture or natural sources (see page 47, lines 1-5 of WO 92/20798). Thus, it is apparent that the extracellular portions set forth in the claims of the above-mentioned application do have a definite and currently available utility for the isolation, characterization and purification of heregulin. For example, using the techniques disclosed in European patent application No. 0 244 221 (copy attached), the extracellular portion of HER2 could be fused to a heterologous reporter polypeptide so that heregulin could be detected and isolated. The extracellular portion of HER2 is also useful in diagnostic radioreceptor assays to measure heregulin binding. Such assays were widely available in the art prior to May 19, 1989.

The extracellular portion of the HER2 receptor, as claimed, is also useful for affinity purification of heregulin, which technique was well known in the art before the filing date of the application. The extracellular portion is coupled to an immobilized resin such as Affi-Gel 10 (Bio-Rad, Richmond, California) or other such resins (support matrices). The resin is equilibrated in a buffer and the preparation to be purified is placed in contact with the resin, whereby the molecules are selectively adsorbed to the receptor on the resin. The resin is then sequentially washed with suitable buffers to remove non-absorbed material, including unwanted contaminants, from the mixture to be purified. The resin is then treated so as to elute the heregulin using a buffer that will break the bond between heregulin and the extracellular domain.

The extracellular portion of the HER2 molecule as claimed in claim 2 and the isolated polypeptide of claim 26 have additional utilities which are inherently disclosed in the application and would have been well known prior to the filing date of the application. In particular, the extracellular portion would be useful for the production of an antibody against the $p185^{HER2}$ extracellular domain. For example, as discussed on page 21 (lines 22-26) and page 22 (lines 1-10) of the application, monoclonal antibodies against the extracellular domain can be made. Claim 2 recites the extracellular portion having

an "immune epitope" and claim 26, as amended, refers to an immune epitope. Hence, it is apparent that the polypeptides encompassed by the claims would be useful for the production of a monoclonal antibody which binds to the extracellular domain of the HER2 receptor. Such antibodies clearly have a definite and currently available utility. For example, the antibodies can be use for affinity purification of the HER2 receptor and in diagnostic assays. For the Examiner's reference, WO 89/06692 is attached which discloses *in vitro* and *in vivo* assays for detecting amplified HER2 expression. See specifically page 22 (line 32) and pages 23 and 24. Since, as discussed on page 21 (lines 15-16), amplified HER2 expression has been correlated with a negative prognosis in breast cancer, such diagnostic assays are certainly useful.

The Examiner asserts (on pages 5-7 of the Office Action) that the specification fails to establish the utility of the claimed extracellular domain and vaccines in the treatment of tumors. Applicants submit that since, as established conclusively above, the utility of the polypeptides has been demonstrated (*e.g.*, for isolating or purifying the ligand thereto and for the manufacture of antibodies against the HER2 receptor), it is not necessary to submit additional data. Furthermore, a vaccine is no longer claimed since claims 22 and 24 now refer to a composition.

Applicants respectfully request that the rejection under 35 USC §101, be reconsidered and withdrawn in light of the above submissions and amendment.

5. The Rejection under 35 USC §112, First Paragraph

The specification is objected to under 35 USC §112, first paragraph, as allegedly failing to provide an enabling disclosure. Claims 2, 3, 5, 7 and 22-27 are rejected for the reasons set forth in the objection to the specification. The Examiner states that the objection is for essentially the reasons discussed in the 101 rejection and cites *In re Ziegler*, 26 USPQ2d 1601 in support of this position. The Examiner has called for evidence of utility.

In the interests of expediting examination, claim 26 has been amended to recite a "secreted HER2 extracellular domain having an immune epitope".

Applicants submit that ample evidence of utility has been presented in the application (see discussion in the preceding section) and thus this rejection should not be maintained. Specifically, the specification enables the use of the extracellular portions for isolating and purifying the ligand and for the manufacture of antibodies thereto. Such ligand isolation/purification techniques and techniques for making antibodies were widely used in the art prior to the above application. Accordingly, the invention as claimed is enabled by the specification as filed.

The Examiner asserts that the evidence of utility must be commensurate in scope with the claims. Applicants submit that the evidence of utility is commensurate in scope with the claims. It is well known in the art that antibodies can be made to peptides having as few as 9 amino acids. For

example, the extracellular portion could have been fused to a hapten and antibodies could have been generated using techniques which were available to the skilled immunologist prior to May 19, 1989. Since independent claim 2 and independent claim 26, as amended, recite that the extracellular portion has an immune epitope, it is apparent that the protein encompassed by the claims would have the required utility insofar as it would enable the production of antibodies thereagainst. It appears the Examiner's primary concerns relate to the use of the protein as a vaccine. However, as established above, since the proteins are useful for the production of antibodies, these concerns are not warranted.

Applicants request that the rejection under 35 USC §112, first paragraph, be reconsidered and withdrawn in light of the above amendments and remarks.

6. The Rejection of Claim 7 under 35 USC §112, Second Paragraph

Claim 7 is rejected under 35 USC §112, second paragraph, as indefinite. Applicants submit that the claim would be sufficiently clear to the skilled immunologist. It is well known in the art that a polypeptide of interest (*e.g.*, the extracellular portion in this instance) can be conjugated to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde or succinic anhydride. These fusion polypeptides are useful for the preparation of antibodies against the protein of interest. Nevertheless, in the interests of expediting examination, claim 7 has been amended to read "a peptide having an immune epitope". Applicants submit that it is well known in the art that an immune epitope is an antigenic determinant to which an antibody binds.

Applicants request that the rejection under 35 USC §112, second paragraph, be reconsidered and withdrawn in light of the amendment.

7. The Rejection under 35 USC §112, Fourth Paragraph

Claims 22 and 24 are rejected as being of improper dependent form. In the interests of expediting examination, these claims have been amended by the incorporation of the dependent claims 23 and 25, respectively therein.

Applicants request that the rejection be withdrawn in light of the amendments.

8. The Rejection under 35 USC §103 - Yamamoto or Coussens in view of Weber, Dull or Dower

Claims 2, 3, 5, 7 and 22-27 are rejected under 35 USC §103 as being unpatentable over Yamamoto *et al.*, *Nature*, **319**: 230-234 (1986) [hereinafter "Yamamoto"] or Coussens *et al.*, *Science*, **230**: 1132-1139 (1985) [hereinafter "Coussens"] each in view of Weber *et al.*, *J. Chromatography*,

431: 55-63 (1988) [hereinafter "Weber"]; US Pat No 5,030,576 [hereinafter "Dull"]; or US Pat No 5,081,228 [hereinafter "Dower"].

The Examiner refers to Yamamoto and Coussens as teaching the nucleotide and amino acids sequences for the HER2 receptor and c-*erbB*-2 and further delineating the extracellular domain thereof. As admitted by the Examiner, these references do not teach production and isolation of the extracellular domain as set forth in the claims. The Examiner refers to the secondary references (*i.e.*, Weber, Dull and Dower) as teaching the advantages of obtaining the soluble extracellular domains of receptor proteins and therefore concludes that it would have been obvious to prepare the soluble extracellular domain of the HER2 receptor. It appears that the Examiner has reasoned that it would have been "obvious to try" to make the extracellular domain as set forth in the claims. However, applicants remind the Office that "obvious to try" is not the standard for patentability under section 103. As stated by the Federal Circuit in *In re O'Farrell et al.*, 7 USPQ2d 1673 (Fed Cir 1988):

> "The admonition that 'obvious to try' is not the standard under [Section] 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g.*, *In re Geiger*, ... 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, ... 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, ... 211 USPQ 1149, 1151 (CCPA 1981); *In re Antoine*, ... 195 USPQ at 8-9. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, ... 5 USPQ2d 1529, 1532 (Fed. Cir. 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* ... 231 USPQ 81, 90-91 (Fed. Cir. 1986) *cert denied* 107 S.Ct. 1606 (1987); *In re Tomlinson*, ... 150 USPQ 623, 626 (CCPA 1966)." 7 USPQ2d at 1681.

Applicants represent that the references relied upon in the Office Action do not teach production and isolation of the HER2 ECD as recited in the claims with the predictability of success required by case law.

In particular, Yamamoto and Coussens discuss the full length sequence for HER2 but do not suggest the production of a protein fragment consisting of the extracellular domain only. Furthermore, these references fail to provide any enabling teaching as to the production and isolation of such a protein fragment.

The secondary references similarly fail to provide any definitive teaching as to the production of the extracellular domain of HER2. Specifically, Webber is concerned with the production of soluble forms of human interleukin-2 receptor (IL-2R) which consists of 251 amino acids (see page 55 of Webber), whereas the HER2 receptor is 1255 residues long; the ECD domain alone is 624 residues long

(see Figure 13 of the application). Accordingly, applicants submit that any teaching with respect to a much smaller protein (*i.e.*, IL-2R) could not have necessarily been extrapolated to the HER2 receptor. In particular, the ability of the larger polypeptide fragment of the above application to be secreted in recombinant cell culture could not have been reasonably predicted based on the teachings of Weber. Also, the methods used to produce the soluble proteins of Weber are notably different from the methods used to isolate the ECD of the HER2 receptor as disclosed in the above application. As mentioned on page 56 of Weber, two secreted forms of the IL-2R were made; one which lacked 28 amino acids at the carboxyl-terminus and had an *added proline* at the carboxyl-terminus, the other which lacked 72 amino acids at the carboxyl-terminus as well as the two naturally occurring N-linked glycosylation sites and had an *additional carboxyl-terminal threonine*. It was found in the instant application, that a truncated $p185^{HER2}$ polypeptide needed to be constructed which terminated upstream of the transmembrane domain in order for the fragment to be secreted from the cells. Surprisingly, the construct lacking the transmembrane domain (and three residues on either side thereof) was not secreted by the cells (see page 13, lines 2-4). Clearly, the residues that needed to be removed from the mature sequence of HER2 in order to create the secreted polypeptide were not taught by Weber. The secreted HER2 ECD construct did not require additional residues at the carboxyl terminus as taught by Weber.

Like IL-2R disclosed by Weber, the interleukin-1 (IL-1) receptor of Dower is much smaller than the mature HER2 receptor. This polypeptide is about 550 residues long (see Fig 3 and 5 of Dower). Also, as disclosed on page 15 (last paragraph) of the above-mentioned application, glycosylation of the HER2 protein can affect its ability to be secreted in recombinant cell culture. Dower showed that the truncated IL-1 receptor was expressed as two different species as determined by their degree of glycosylation. Accordingly, the ordinarily skilled practitioner could not have predicted the ability of the HER2 ECD to be successfully expressed and secreted, because the glycosylation pattern of the protein could have affected its ability to be secreted.

Dull discloses a fusion of a ligand binding domain and a heterologous reporter polypeptide, but does not disclose production of the ECD domain only. Like the other secondary references, this reference fails to address the ability of the HER2 ECD to be secreted from microbial cell culture, taking into account that glycosylation may prevent the truncated polypeptide from being secreted.

Applicants further note that the primary and secondary references fail to provide any motivation as to the provision of the isolated ECDs in an immune adjuvant, as recited in claims 22 and 24, as amended. In example 7 of Dower, the native protein, not the truncated ECD, was emulsified in Freund's adjuvant.

Since the primary and secondary references fail to provide the appropriate teaching for the production and isolation of HER2 ECD as recited in the claims, applicants submit that the invention

claimed is clearly unobvious over the references. Reconsideration of the rejection under 35 USC § 103 is respectfully solicited.

9. The Rejection under 35 USC §103 - Yamamoto or Coussens in view of Bernards and further in view of Maddon, Hudziak or Masuko

Claims 2, 3, 5, 7 and 22-27 are rejected under 35 USC §103 as being unpatentable over Yamamoto or Coussens each in view of Bernards *et al.*, *PNAS*, **84**: 6854-8 (1987) [hereinafter "Bernards"] and further in view of US Pat No 5,126,433 [hereinafter "Maddon"]; Huziak *et al.*, *Mol. Cell. Biol.*, **9(3)**: 1165-72 (1989) [hereinafter "Hudziak"]; or Masuko *et al.*, *Jpn. J. Cancer Res.*, **80**: 10-14 (1989) [hereinafter "Masuko"].

The primary references (Yamamoto and Coussens) are cited as delineating the ECD of the HER2 receptor. Again, the Office acknowledges that these references do not teach production of the ECD without the transmembrane and cytoplasmic domains. Accordingly, the Examiner cites Bernards (the secondary reference) as teaching expression of the rat homolog of HER2 (*i.e.*, neu) in a form lacking the majority of the cytoplasmic domain. As pointed out by the Examiner, this truncated polypeptide is not soluble insofar as it still retains the transmembrane domain of the native protein. Since neither the primary or secondary references disclose or suggest expression of the truncated ECD of the HER2 receptor, the Examiner further cites the tertiary references (Maddon, Hudziak and Masuko). Maddon is said to teach that a soluble receptor may be used as a therapeutic agent or to raise antibodies which may be useful for therapy. Hudziak and Masuko are cited on the basis that these references refer to the production of MAbs against the HER2 receptor. The Examiner urges that, based on these references, it would have been *prima facie* obvious to prepare a soluble extracellular domain of the HER2 receptor as one would have been motivated to do so in that it may be used as a vaccine (as taught by Bernards) or to prepare MAbs. The Examiner further asserts that one would have expected the recombinant ECD to have such uses in view of Maddon. Applicants respectfully traverse this rejection.

As mentioned above, "obvious to try" is not the standard for patentability under section 103. Applicants submit that the references relied upon in the Office Action do not teach production of the HER2 ECD as recited in the claims with the predictability of success required by case law.

As addressed in the preceding section of this amendment, neither Yamamoto or Coussens provided any motivation or enabling disclosure as to the production of the ECD of the HER2 receptor.

As the Examiner has acknowledged, Bernards is concerned with a truncated protein which is different from that recited in the claims of the above application. Not only is the truncated protein of Bernards derived from a rat (whereas the HER2 receptor is from a human), but the truncated version of the neu protein disclosed in Bernards has the transmembrane domain (see Fig 1) and part of the

cytoplasmic domain. The polypeptide recited in the claims of the above application is a soluble protein and specifically excludes the transmembrane and cytoplasmic domain of the mature protein. Accordingly, Bernards teaches away from the invention recited in the claims of the above application and would clearly have failed to provide any motivation to make the secreted protein of the claims, much less any guidance as to the production of such a secreted protein. The Examiner makes the assertion that it would have been *prima facie* to use the HER2 ECD as a vaccine based on Bernards.

Applicants are unable to agree with the Examiner in this respect. First, neu and the HER2 receptor differ in primary and secondary structures; they are derived from different species. Furthermore, Bernards' data is concerned with immunizing mice with a membrane-bound version of neu which has the transmembrane domain thereof. On the contrary, the polypeptide of the instant application does not have the transmembrane domain of HER2 receptor and is therefore soluble. Accordingly, Bernards would not have provided any motivation to manufacture the polypeptide of the claims of the above application or the vaccine recited in claims 22 and 24 (as amended).

Maddon relates to soluble forms of the CD4 receptor protein, which is unrelated to the HER2 receptor. Applicants submit that this reference could not have been predictive as to the production of soluble, secreted HER2 ECD as set forth in the claims of the above application. The two proteins clearly have different primary and secondary structures. Importantly, the glycosylation patterns of these proteins are different (see Figure 6 and description thereof in column 4 of Maddon, and page 15, lines 14-17 of the above application) and, as shown in the present application, glycosylation can prevent secretion of the HER2 receptor polypeptide of the above application. Therefore, based on the teachings of Maddon, the ordinarily skilled practitioner could not have guessed that HER2 ECD could have been isolated, with the requisite predictability of success.

Hudziak and Masuko similarly fail to motivate or provide direction to the skilled practitioner as to the production of the isolated ECD as recited in the claims of the above application. In Hudziak, antibodies (directed against the ECD) were generated against the native receptor sequence, not the isolated ECD. Cells expressing high levels of the HER2 receptor were used to immunize mice (see page 1165, second column). Masuko also made a MAb which recognizes an ECD of the HER2 receptor. The techniques used by Masuko were similar to Hudziak; mice were immunized against SV11 cells in which the full length c-*erbB*-2 cDNA is expressed (see page 10, second column). Accordingly, these references would not have motivated the skilled practitioner to isolate a fragment of the HER2 receptor consisting only of the ECD, since these references show that the entire sequence of the HER2 receptor is required for the production of antibodies thereagainst. Indeed, these references would have taught away from the production of the truncated protein, where use of the protein for the production of antibodies against the HER2 receptor was contemplated. Furthermore, these references do not provide

enabling disclosure as to the production of HER2 ECD and fail to address the difficulties which may have been encountered in any attempt to make such a fragment.

In summary, it is apparent that the primary, secondary and tertiary references relied upon by the Examiner in the rejection of the claims under 35 USC §103 would not have rendered the claimed invention obvious. Applicants ask that the rejection of the claims be reconsidered and withdrawn in light of the above submissions.

As all rejections have been addressed and overcome, applicants believe that the claims are now in condition for allowance. Notice to that effect is respectfully requested.

A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the undersigned to prosecute the above-mentioned application. The original of this document is on file in the Office of Enrollment and Discipline.

Respectfully submitted,
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Attachments
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